REMARKS

Claims 20, 28, 30, 32, 33, 35, and 39-48 were pending in the application. Claims 28, 39-42, and 45-48 have been cancelled without prejudice to presentation in future related applications. Claims 20, 30, 35, 43, and 44 have been amended for further grammatical clarity and/or to recite that the nucleic acid has the nucleotide sequence of SEQ ID NO:1587. No new matter has been added. Upon entry of this amendment, claims 20, 30, 32, 33, 35, 43 and 44 will be pending.

Applicants respectfully request reconsideration and allowance of claims 20, 30, 32, 33, 35, 43 and 44 in view of the above amendments and following remarks.

Withdrawal of Previous Rejections

Applicants acknowledge with appreciation the withdrawal of the following:

a) rejection of claim 42 under 35 U.S.C., §112, first paragraph; and

b) rejection of claims 20, 28, 30, 32, 33, 35, and 39-42 under 35 U.S.C., §112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph

The Office rejected claims 20, 28, 30, 32, 33, 35, 39-42, and 45-48 under 35 U.S.C. §112, first paragraph, for lack of enablement. The Office asserted that a copy of the second Tockman reference (Clin. Can. Res. 3:2237-2246, 1997) was not provided by Applicants in the previous response and from Applicants' description of the reference, "it appears that it does not contain any data or teachings that contradict the assertion that the art of cancer diagnosis is unpredictable." A copy of the Tockman reference is attached for the Examiner's review.

Claim 28, 39-42, and 45-48 have been canceled without prejudice. Claims 20, 30, 32, 33, and 35 recite that the nucleic acid has the nucleotide sequence of SEQ ID NO:1587. As noted by the Office on page 8 of the Office Action, the specification is enabled for methods where the expression product that is detected is an mRNA having the sequence of SEQ ID NO:1587.

The Office on page 7 alleged that the Kihara reference and Padma reference "teaches that a change in calcineurin activity not protein or mRNA levels is associated with leukemia." The claimed methods, however, do not relate to diagnosing leukemia.

In light of the above, the Office is requested to withdraw the rejection of claims 20, 30, 32, 33, and 35 under 35 U.S.C. §112, first paragraph.

The Office rejected claims 43 and 44 under 35 U.S.C. §112, first paragraph, for lack of written description. The Office alleged that the phrase "PPP3CC protein" was interpreted as "having an embodiment of amino acid variants of the naturally occurring sequences, where preferably the variants are greater than about 75% homologous to the wild type sequence." With respect to claim 44, which recites 98% sequence identity, the Office alleged that the "specification fails to provide support because while the protein encoded by SEQ ID NO:1587 may be diagnostic of colon cancer, there is no evidence or line of reasoning presented in the specification that any variants of such proteins are diagnostic of colon cancer." Applicants disagree.

Amended claim 43 recites that the PPP3CC protein is encoded by a nucleic acid having the nucleotide sequence set forth in SEQ ID NO:1587. As indicated by the Office on page 11 of the Office Action, the protein encoded by SEQ ID NO:1587 is diagnostic of cancer. The Office is requested to withdraw the rejection of claim 43 under 35 U.S.C. §112, first paragraph, for an alleged lack of written description.

With respect to claim 44, Applicants submit that claim 44 has written description sufficient to satisfy the MPEP, the Written Description Guidelines, and the relevant case law. An adequate description is one that describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Possession may be shown in a variety of ways. For example, possession can be found where an Applicant presents drawings of the claimed invention (as in *Vas-Cath*) or structural chemical formulas. An Applicant may also describe distinguishing identifying characteristics. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55 (1998); *Amgen, Inc. v. Chugai Pharm.*, 927 F.2d 1200 (Fed. Cir. 1991) (one may define a compound by "whatever characteristics sufficiently distinguish it").

With respect to the number of species disclosed, the Written Description Guidelines from the January 2001 *Federal Register* (at page 1106, emphasis added) state:

> Satisfactory disclosure of a "representative number" [of species] depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

Although neither the PTO nor the Federal Circuit has provided specific guidance on exactly how many species constitute a "representative number of species," Applicants respectfully assert that the nucleic acid of SEQ ID NO:1587 is representative of the genus of sequences – i.e. nucleic acids having at least 98% sequence identity to the sequence of SEQ ID NO:1587 that are diagnostic of cancer. The nucleic acid of claim 44 is defined structurally, *i.e.*, contains a highly similar nucleotide sequence. For example, each and every one of the species encompassed by the genus of claim 44 must include a sequence at least 98% identical to SEQ ID NO:1587. Furthermore, the present specification describes variants and methods of making them (see, e.g., paragraphs [0094]-[0098]). Accordingly, Applicants have described the necessary common attributes of *all* of the sequences claimed.

The nucleic acids of claim 44 are also in accordance with Revision 1 of the Written Description Training Materials (March 25, 2008). See, Examples 10 and 11A. All of the species within the genus share a significant degree of partial structure (i.e., at least 98% of SEQ ID NO:1587). Applicants note that the level of identity recited in the present claims is higher than that of Example 11A of the Written Description Training Materials (85%), thereby further decreasing any potential variation between species. With the aid of a computer, one of ordinary skill can easily and with 100% predictability envision every possible sequence that satisfies the criteria of the claimed genus. Thus, the specification describes 98% of the structure that defines the nucleic acids within the claimed genus.

Given Applicants' description in the specification, one of ordinary skill in the art would have no difficulty in envisioning all of the claimed species and would conclude that Applicants were in possession of those nucleic acids. Thus, in view of the specification and knowledge in the art, one of ordinary skill would have realized that the inventors provided a representative number of species within the genus of nucleic acid sequences having at least 98% identity to

SEQ ID NO:1587. Accordingly, the Office is requested to withdraw the rejection under 35 U.S.C. §112, first paragraph, for an alleged lack of written description.

Rejection under 35 U.S.C. §112, second paragraph

The Office rejected claims 30 and 39 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite in the recitation of "known normal tissue" or "known sample comprising normal tissue." The Office asserted that the word "known" is a relative term.

Claim 39 has been cancelled. Amended claim 30 recites that the control is non-cancerous and of the same tissue type as the patient's sample. The Office is requested to withdraw the rejection of claim 30 under 35 U.S.C. §112, second paragraph.

The Office rejected claim 35 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite as the gene is not specified in step a). The Office further asserted that the full complement is not an expression product of the same gene.

Claim 35 has been amended to delete the phrase "or a full complement thereof" and to indicate the expression level of a nucleic acid having the nucleotide sequence of SEQ ID NO:1587 is determined. The Office is requested to withdraw the rejection of claim 35 under 35 U.S.C. §112, second paragraph.

The Office rejected claim 42 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because it refers to an expression product that has "the same expression profile as SEQ ID NO:1587." The Office asserted that "[t]his appears to be incorrect usage of the phrase 'expression profile' which is a phrase used to denote the expression levels found in a particular sample of a plurality of genes or proteins."

This rejection is moot as claim 42 has been cancelled.

The Office rejected claims 43 and 44 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because the comparison sample is not specified.

Claims 43 and 44 have been amended to recite that the sample is compared to a non-cancerous colon control sample. The Office is requested to withdraw the rejection of claims 43 and 44 under 35 U.S.C. §112, second paragraph.

The Office rejected claim 45 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite in the recitation of "highly stringent conditions." This rejection is moot as claim 45 has been cancelled.

The Office rejected claim 39, 45, and 46 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for reciting that the method is for diagnosing prostate, stomach, and breast cancer rather than reciting the cancers in the alternative.

This rejection is moot as claims 39, 45, and 46 have been cancelled.

The Office rejected claim 48 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for lacking antecedent basis for "colon cancer."

This rejection is moot as claim 48 has been canceled.

Rejections under U.S.C. §102

The Office rejected claims 43 and 44 under 35 U.S.C. §102(b) as being anticipated by McGarrity (Gut, 32:1121-1126, 1991) as evidenced by Billingsley (Proc. Natl. Acad. Sci., USA, 82:7585-7589, 1985). The Office alleged that the intended use of the method of claims 43 and 44 is to diagnose colon cancer but the intended use does not appear to affect the nature of the method steps. The Office further alleged that

> McGarrity teaches detection of a 67 kDa calmodulin-binding protein in human colon and colon cancer samples (see Figure 2). McGarrity teaches that this 67 kDa protein may be calcineurin, which is another name for PPP3CC. Billingsley teaches that human calcineurin appears to have a molecular weight of about 61 kDa (see abstract). However, in Figure 3, (page 7588), it appears using the same method as that used in McGarrity, that standard calcineurin has a molecular weight closer to 67 kDa (see Figure 3, lane 8 and legend). Therefore, absent evidence to the contrary, it appears that McGarrity teaches a method that is the same as that claimed.

Applicants disagree.

The McGarrity reference discloses that a calmodulin binding protein having a molecular weight of 67 kDa can be detected in membrane and cytosolic fractions of eosophagus, stomach, proximal and distal small intestine, and colon from humans, rabbits, rats, and mice. McGarrity indicates on page 1125 that "[a]lthough the identity of the 67 kDa protein is not known, possibilities include subunits of calmodulin kinase II, calcineurin, or a novel binding protein found primarily in gastrointestinal tissue."

The abstract of the Billingsley reference discloses that when purified calcineurin was subjected to one- and two-dimensional gel electrophoresis and protein blotting, only the 61 kDa calmodulin-binding subunit was detected. The abstract further indicates that there are several apparent forms of the 61 kDa catalytic subunit, consistent with isozymic species of the enzymes. On page 7587, the Billingsley reference discloses that calcineurin appeared as a single band of 60 kDa after protein staining. Thus, the overall conclusion of the Billingsley reference is that the catalytic domain of calcineurin has a molecular weight around 60 to 61 kDa.

The Office concludes differently from Billingsley et al. and alleges that the molecular weight of calcineurin is "closer to 67 kDa." Such a conclusion, however, is not supported by the text of the Billingsley et al. reference ,or by the Lakshmikuttyamma reference (J. Cellular Biochem. 95:731-739 (2005); cited by the Office in the Office Action of December 15, 2006) or Kihara et al reference (Int. J. Oncol. 12:629-634 (1998); cited by the Office in the Office Action of December 15, 2006). The Lakshmikuttyamma reference and Kihara et al. reference indicate that the catalytic subunit has an apparent molecular mass of 60 kDa.

Since the identity of the protein detected by McGarrity is not known and has a molecular weight that differs from calcineurin, the McGarrity reference does not anticipate the methods of claims 43 and 44. The Office is requested to withdraw the rejection of claims 43 and 44 under 35 U.S.C. §102(b).

The Office rejected claims 35, 39-42, and 45-47 under 35 U.S.C. §102(e) as being anticipated by Bertucci (U.S. Publication No. 20030143539). The Office asserted that Bertucci teaches a sequence that is identical to the sequence of SEQ ID NO:1587.

Claims 39-42 and 45-47 have been canceled. Amended claim 35 does not recite a method for detecting breast cancer. As such, the Bertucci publication does not anticipate claim 35 and the Office is requested to withdraw the rejection under 35 U.S.C. §102(e).

CONCLUSION

It is believed that any pending objections and rejections have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims

(or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Applicants submit that claims 20, 30, 32, 33, 35, 43 and 44 are in condition for allowance, which action is requested. Please charge Deposit Account No. 06-1050 for a 2-month Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: June 23, 2008

/Monica McCormick Graham/
Monica McCormick Graham, Ph.D.
Reg. No. 42,600

Fish & Richardson P.C.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696